UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/410,319	10/01/1999	ALEXEY VLADIMIROVICH TITIEVSKY	CEPH-0866	6692

7590 05/06/2003

DOREEN YATKO TRUJILLO
WOODCOCK WASHBURN KURTZ MACKIEWICZ
& NORRIS LLP
ONE LIBERTY PLACE 46TH FLOOR
PHILADELPHIA, PA 19103

EXAMINER	
CHAKRABARTI, ARUN K	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 05/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/410,319	Titievsky et al.
Examiner	**Art Unit**
Arun Chakrabarti	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 24, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-91* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-91* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

DETAILED ACTION

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 1-6, 16- 21, 30, 32, 39, 40 and 42 are rejected under 35 U.S.C. 103 (a) over Ibanez et al. (PCT International Application Number WO 97/18240) (May 22, 1997) in view of Jefferies et al. (U.S. Patent 5,981,194) (November 9, 1999) further in view of Baloh et al. (Proc. Natl. Acad. Sci. (USA), (1998), Vol. 95, pages 5801-5806).

Ibanez et al teach a method for identifying GDNF analogs that is an agonist of intracellular signaling effected by c-RET receptors in nervous system cells comprising (I) incubating the

nervous system cells having c-RET receptors with a test compound and (ii) determining whether intracellular signaling has been effected in the cells (Claims 10, 16 and 18).

Ibanez et al teach a method wherein the nervous system cells are neuroblastoma cells (Claims 11, 17 and 19).

Ibanez et al do not teach a method for identifying an antagonist of intracellular signaling effected by c-RET receptors in nervous system cells comprising (I) incubating the nervous system cells having c-RET receptors with a test compound and (ii) determining whether intracellular signaling has been effected in the cells.

Jefferies et al teach a method for identifying a compound that is an agonist or antagonist of intracellular signaling effected by GPI-anchored receptors in nervous system cells comprising (I) incubating the nervous system cells having GPI-anchored receptors with a test compound and (ii) determining whether intracellular signaling has been effected in the cells (Column 8, lines 30-48 and Column 25, lines 38-58).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the antagonist of intracellular signaling detection of Jefferies et al. in the method of identifying compounds of Ibanez et al., since Jefferies et al. state, "Accordingly, substances may be identified which are effective in the treatment of Alzheimer's disease (Column 10, lines 56-58)." An ordinary practitioner would have been motivated to combine and substitute the antagonist of intracellular signaling detection of Jefferies et al. in the method of identifying compounds of Ibanez et al., in order to achieve the express

advantages noted by Jefferies et al of an invention which supports the identification of substances effective in the treatment of Alzheimer's disease.

Ibanez et al in view of Jefferies et al. do not teach a method wherein GDNF is linked to GPI-anchored proteins.

Baloh et al. teach a method wherein GDNF is linked to GPI-anchored proteins (Abstract and RESULTS Section).

Ibanez et al in view of Jefferies et al. do not teach a method wherein the nervous system cells express GFRalpha1 receptors but not Ret receptors.

Baloh et al. teach a method wherein the nervous system cells express GFRalpha receptors but not Ret receptors. (Abstract, Introduction, last two paragraphs).

Ibanez et al in view of Jefferies et al. do not teach a method wherein the nervous system cells are DRG neurons Ret (-/-) and Ret-independent.

Baloh et al. teach a method wherein the nervous system cells are DRG neurons Ret (-/-) and Ret-independent (Discussion Section, Page 5806, Column 1, second paragraph).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the GDNF- linked to GPI-anchored proteins GFRalpha receptors wherein the nervous system cells are DRG neurons Ret (-/-) and Ret-independent of Baloh et al. in the method of identifying compounds of Ibanez et al. in view of Jefferies et al., since Baloh et al. state, "Our analysis of transfected fibroblasts indicates that GFRalpha3 does not form a functional receptor complex with Ret for any of the known GF

ligands. There are several possibilities to explain this result, all of which suggest the presence of additional receptor system components. We cannot exclude the possibility that known GF ligands interact with GFRalpha3 in the presence of another Ret like signaling protein. The existence of another Ret like signaling molecule has also been proposed to explain the expression of GFRalpha1 and GFRalpha2 in several structures without Ret (Page 5806, Column 1, lines 9-18)". An ordinary practitioner would have been motivated to combine and substitute the GDNF-linked to GPI-anchored proteins GFRalpha1 receptors of Baloh et al. in the method of identifying compounds of Ibanez et al. in view of Jefferies et al., in order to achieve the express advantages noted by Baloh et al of an invention which indicates that GFRalpha3 does not form a functional receptor complex with Ret for any of the known GF ligands raising several possibilities, all of which suggest the presence of additional receptor system components other than Ret signaling protein to explain the expression of GFRalpha1 and GFRalpha2 in several structures without Ret.

3. Claims 1-10, 15- 24, 29-33, 38-40, 42 , 43 and 48-58 are rejected under 35 U.S.C. 103 (a) over Ibanez et al. (PCT International Application Number WO 97/18240) (May 22, 1997)in view of Jefferies et al. (U.S. Patent 5,981,194) (November 9, 1999) further in view of Baloh et al. (Proc. Natl. Acad. Sci. (USA), (1998), Vol. 95, pages 5801-5806) further in view of Shen et al. (Journal of Immunology, (1994), Vol. 152, pages 3017-3023).

Ibanez et al. in view of Jefferies et al. further in view of Baloh et al teach methods of claims 1-6, 16- 21, 30, 32, 39, 40 and 42 as described above.

Ibanez et al. in view of Jefferies et al. further in view of Baloh et al do not teach the method wherein the intracellular signaling is measured as an increase in intracellular Calcium concentration as compared to controls not incubated with the compound.

Shen et al teach the method wherein the intracellular signaling is measured as an increase in intracellular Calcium concentration as compared to controls not incubated with the compound. (Abstract and Figure 4 and Materials and Methods Section, Ca 2+ flux assay subsection).

Ibanez et al. in view of Jefferies et al. further in view of Baloh et al do not teach the method wherein the intracellular signaling is measured as kinase activation by (I) preparing a cell lysate, (ii) immunoprecipitating the cell lysate with an anti GPI-anchored antibody to form an immunoprecipitate, (iii) performing an assay to measure kinase phosphorylation on the immunoprecipitate, and (iv) comparing the results with controls not incubated with the compound.

Shen et al teach the method wherein the intracellular signaling is measured as kinase activation by (I) preparing a cell lysate, (ii) immunoprecipitating the cell lysate with an anti GPI-anchored antibody to form an immunoprecipitate, (iii) performing an assay to measure kinase phosphorylation on the immunoprecipitate, and (iv) comparing the results with controls not incubated with the compound. (Abstract, Materials and Methods Section, Immunoprecipitation subsection and Figures 1-3).

Ibanez et al. in view of Jefferies et al. further in view of Baloh et al do not teach the method wherein the kinase is measured as PLCgamma activation.

Shen et al teach the method wherein the kinase is measured as PLCgamma activation. (Abstract and Figures 3 and 5)

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the intracellular signaling measurement by an increase in intracellular Calcium concentration and PLCgamma activation and Immunoprecipitation of Shen et al. in the method of identifying compounds of Ibanez et al. in view of Baloh et al , since Shen et al. state, "Activation of protein tyrosine kinase after ligand binding has been shown to be the primary event for signaling by members of the multichain immune recognition receptor family (Page 3022, column 1, lines 8-11)." An ordinary practitioner would have been motivated to combine and substitute the intracellular signaling measurement by an increase in intracellular Calcium concentration and PLCgamma activation and Immunoprecipitation of Shen et al. in the method of identifying compounds of Ibanez et al. in view of Baloh et al, in order to improve the identification method of a compound that is an agonist or antagonist of intracellular signaling effected by GPI-anchored receptors in nervous system cells and also in order to achieve the express advantages noted by Shen et al., of a biochemical pathway i.e., activation of protein tyrosine kinase after ligand binding that has been shown to be the primary event for signaling by members of the multichain immune recognition receptor family.

4. Claims 1-10, 12- 13, 15-24, 26-27, 29-33, 35-36, 38-40, 42 , 43, 45-46, 48-58 , 68, 69, 70, 75, 76, 77, 79-82, 83-85, 87-89 and 91 are rejected under 35 U.S.C. 103 (a) over Ibanez et al.

(PCT International Application Number WO 97/18240) (May 22, 1997) in view of Jefferies et al. (U.S. Patent 5,981,194) (November 9, 1999) further in view of Baloh et al. (Proc. Natl. Acad. Sci. (USA), (1998), Vol. 95, pages 5801-5806) further in view of Shen et al. (Journal of Immunology, (1994), Vol. 152, pages 3017-3023) further in view of Dikic et al. (Nature, (1996), Vol. 383, pages 547-549).

Ibanez et al. in view of Jefferies et al. further in view of Baloh et al further in view of Shen et al. teach methods of claims 1-10, 15- 24, 29-33, 38-40, 42 , 43 and 48-58 as described above.

Ibanez et al. in view of Jefferies et al. further in view of Baloh et al further in view of Shen et al do not teach the method wherein the kinase is Src-type kinase that is measured by activation of MAPK.

Dikic et al. teach the method wherein the kinase is Src-type kinase that is measured by activation of MAPK. (Abstract, Figure 4 and Methods Section, Kinase Assays subsection).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the Src-type kinase that is measured by activation of MAPK of Dikic et al. in the method of identifying compounds of Ibanez et al. in view of Jefferies et al. further in view of Baloh et al further in view of Shen et al., since Dikic et al. state, "Src family protein tyrosine kinases, which are expressed in every cell type and tissue, appear to be a common and important component of this pathway, acting together with cell-type-specific protein tyrosine kinases, such as Pyk2 in PC12 cells or Syk in avian B cells, to bring about a cell-type-specific signal for linking G-protein coupled receptors with the MAP kinase

signaling pathway and hence the transcriptional machinery (Page 549, Column 2, last sentence)." An ordinary practitioner would have been motivated to combine and substitute the Src-type kinase that is measured by activation of MAPK of Dikic et al. in the method of identifying compounds of Ibanez et al. in view of Jefferies et al. further in view of Baloh et al further in view of Shen et al., in order to improve the identification method of a compound that is an agonist or antagonist of intracellular signaling effected by GPI-anchored receptors in nervous system cells and also in order to achieve the express advantages , as noted by of Dikic et al , of the Src family protein tyrosine kinases, which are expressed in every cell type and tissue, appear to be a common and important component of this pathway, acting together with cell-type-specific protein tyrosine kinases to bring about a cell-type-specific signal for linking G-protein coupled receptors with the MAP kinase signaling pathway and hence the transcriptional machinery.

5. Claims 1-10, 12-24, 26-33, 35-40, 42 , 43, 45-58 , 68, 69, 70, 71, 75, 76, 77-82, 83-89 and 90-91 are rejected under 35 U.S.C. 103 (a) over Ibanez et al. (PCT International Application Number WO 97/18240) (May 22, 1997) in view of Jefferies et al. (U.S. Patent 5,981,194) (November 9, 1999) further in view of Baloh et al. (Proc. Natl. Acad. Sci. (USA), (1998), Vol. 95, pages 5801-5806) further in view of Shen et al. (Journal of Immunology, (1994), Vol. 152, pages 3017-3023) further in view of Dikic et al. (Nature, (1996), Vol. 383, pages 547-549) further in view of Finkbeiner et al. (Neuron, (1997), Vol. 19, pages 1031-1047).

Ibanez et al. in view of Jefferies et al. further in view of Baloh et al further in view of Shen et al. further in view of Dikic et al teach methods of claims 1-10, 12- 13, 15-24, 26-27, 29-

33, 35-36, 38-40, 42 , 43, 45-46, 48-58 , 68, 69, 70, 75, 76, 77, 79-82, 83-85, 87-89 and 91 described above.

Ibanez et al. in view of Baloh et al in view of Jefferies et al. further in view of Shen et al further in view of Dikic et al do not teach the method wherein the activation of Src-type kinase is measured as activation of CREB.

Finkbeiner et al. teach the method wherein the activation of Src-type kinase is measured as activation of CREB(Abstract and Figures 2, 10 and 12).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the activation of Src-type kinase that is measured as activation of CREB of Finkbeiner et al. in the method of identifying compounds of Ibanez et al. in view of Jefferies et al. further in view of Baloh et al further in view of Shen et al. further in view of Dikic et al, since Finkbeiner et al. state, "These findings reveal a previously unrecognized, CaMK-dependent mechanism by which neutrophins activate CREB and suggest that CREB plays a central role in mediating neutrophin responses in neurons (Abstract, last sentence)." An ordinary practitioner would have been motivated to combine and substitute the activation of Src-type kinase that is measured as activation of CREB of Finkbeiner et al. in the method of identifying compounds of Ibanez et al. in view of Jefferies et al. further in view of Baloh et al further in view of Shen et al. further in view of Dikic et al, in order to improve the identification method of a compound that is an agonist or antagonist of intracellular signaling effected by GPI-anchored receptors in nervous system cells and also in order to achieve the

express advantages, as noted by Finkbeiner et al., of CREB that plays a central role in mediating neutrophin responses in neurons.

6. Claims 1-91 are rejected under 35 U.S.C. 103 (a) over Ibanez et al. (PCT International Application Number WO 97/18240) (May 22, 1997) in view of Jefferies et al. (U.S. Patent 5,981,194) (November 9, 1999) further in view of Baloh et al. (Proc. Natl. Acad. Sci. (USA), (1998), Vol. 95, pages 5801-5806) further in view of Shen et al. (Journal of Immunology, (1994), Vol. 152, pages 3017-3023) further in view of Dikic et al. (Nature, (1996), Vol. 383, pages 547-549) further in view of Finkbeiner et al. (Neuron, (1997), Vol. 19, pages 1031-1047) further in view of Chalazonitis et al. (Developmental Biology, (1998), Vol. 204, pages 385-406).

Ibanez et al. in view of Jefferies et al. further in view of Baloh et al further in view of Shen et al. further in view of Dikic et al further in view of Finkbeiner et al. teach methods of claims 1-10, 12-24, 26-33, 35-40, 42 , 43, 45-58 , 68, 69, 70, 71, 75, 76, 77-82, and 83-91 as described above.

Ibanez et al. in view of Jefferies et al. further in view of Baloh et al further in view of Shen et al further in view of Dikic et al further in view of Finkbeiner et al. do not teach the method wherein the antibody is anti-GFRalpha1.

Chalazonitis et al teach the method wherein the antibody is anti-GFRalpha1 (Figures 12, 15 and Materials and Methods Section, Immunocytochemistry Subsection).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the antibody assay using anti-GFRalpha1 of

Chalazonitis et al. in the method of identifying compounds of Ibanez et al. in view of Jefferies et al. further in view of Baloh et al further in view of Shen et al. further in view of Dikic et al further in view of Finkbeiner et al., since Chalazonitis et al. state, "The number of GFRalpha-1 immunoreactive cells in cultures was found in the current study to be greatly increased by exposure to GDNF, an effect that could be explained by an ability of GDNF to enhance the expression of its own receptor. Alternatively, the GDNF-induced increase in GFRalpha-1 immunoreactive cells may simply reflect the enhanced development in the presence of GDNF of neurons, which are the cells that anchor GFRalpha-1 (Page 401, column 1, last paragraph to column 2, line 8)." An ordinary practitioner would have been motivated to combine and substitute the antibody assay using anti-GFRalpha1 of Chalazonitis et al. in the method of identifying compounds of Ibanez et al. in view of Jefferies et al. further in view of Baloh et al further in view of Shen et al. further in view of Dikic et al further in view of Finkbeiner et al., in order to improve the identification method of a compound that is an agonist or antagonist of intracellular signaling effected by GPI-anchored receptors in nervous system cells and also in order to achieve the express advantages, as noted by Chalazonitis et al., of an antibody that can detect the ability of GDNF to enhance the expression of its own receptor.

Response to Arguments

7. Applicant's arguments with respect to all pending claims have been considered but are they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant also argues that there is no motivation to combine the references. This argument is not persuasive, especially in the presence of strong motivation provided by Finkbeiner et al. since Finkbeiner et al. state, "These findings reveal a previously unrecognized, CaMK-dependent mechanism by which neutrophins activate CREB and suggest that CREB plays a central role in mediating neutrophin responses in neurons (Abstract, last sentence)." The same logic is applicable to other combinatory references as well.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant then argues the 103 rejection is improper because it lacks a reasonable expectation of success.

With regard to the "lacks a reasonable expectation of success" argument, The MPEP 2143.02 states, "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart , 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) (Claims directed to a method for the commercial scale production of polyesters in the presence of a solvent at superatmospheric pressure were rejected as obvious over a reference which taught the claimed method at atmospheric pressure in view of a reference which taught the claimed process except for the presence of a solvent. The court reversed, finding there was no reasonable expectation that a process combining the prior art steps could be successfully scaled up in view of unchallenged evidence showing that the prior art processes individually could not be commercially scaled up successfully.). See also Amgen, Inc. v. Chugai Pharmaceutical Co ., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir.), cert. denied , 502 U.S. 856 (1991) (In the context of a biotechnology case, testimony supported the conclusion that the references did not show that there was a reasonable expectation of success. 18 USPQ2d at 1022, 1023.); In re O'Farrell , 853 F.2d 894, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.)."

There is no evidence of record submitted by applicant demonstrating the absence of a reasonable expectation of success. There is evidence in the Baloh reference of the enabling

methodology, the suggestion to modify the prior art, and evidence that a number of different cells that do not express Ret, were actually experimentally studied and found to be functional (Discussion Section, Page 5806, Column 1, second paragraph). This evidence of functionality trumps the attorney arguments, which argues that Baloh reference is an invitation to research, since Baloh steps beyond research and shows the functional product.

Applicant argues that Baloh reference does not teach the Ret independent pathway of the claimed invention. Applicant argues that the word "Ret (-/-)" was not found in Baloh reference and only the sentence "Ret-like signalling may be involved" is found. Applicant argues that because Baloh has a preferred embodiment of speculation of the Ret independent pathway, Baloh is limited to the preferred embodiment. This argument is not persuasive. As MPEP 2123 states "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi,169 USPQ 423 (CCPA 1971)." MPEP 2123 also states " A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories , 10 USPQ2d 1843 (Fed. Cir. 1989)." It is clear that simply because Baloh has a preferred embodiment, this embodiment does not prevent the reference from suggesting broader embodiments in the disclosure and that this does not constitute a teaching away. Although Baloh reference uses the assumption that some cells do not express Ret, the property of Ret (-/-) in this chemically and structurally identical molecule. For example,Baloh teaches that a number of different cells that do not express Ret, were actually experimentally

studied and found to be functional (Discussion Section, Page 5806, Column 1, second paragraph). Moreover, MPEP 2111 states, "Claims must be given their broadest reasonable interpretation. During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification". Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than it is justified. *In re Prater,* 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-51 (CCPA 1969)". In this case, any cells of nervous system that express GFRalpha receptors but not Ret receptors, as taught by Baloh, meets the requirement of the claims.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703) 306-5818.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)308-1119.

Any inquiry of general nature or relating to the status of this application should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Arun Chakrabarti,

Patent Examiner

Art Unit 1634

April 22, 2003

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600